(FILE 'HOME' ENTERED AT 16:40:04 ON 06 FEB 2002)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF'
ENTERED AT 16:40:22 ON 06 FEB 2002

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L1        185321 S TRANSGENIC
L2        107446 S L1 AND (RAT OR MICE)
L3          4832 S L2 AND (SV40? OR MMTV? OR NEUROFILAMENT? OR NF-L)
L4           298 S L3 AND (TGF? OR ERB?)
L5           125 DUP REM L4 (173 DUPLICATES REMOVED)
L6            53 S L5 AND PY<=1996
L7            53 SORT L6 PY
L8             0 S L7 AND (TRANSGENIC RAT)
L9          2679 S TRANSGENIC RAT
L10           19 S L9 AND (MMTV? OR NEUROFILAMENT? OR NF-L)
L11            7 DUP REM L10 (12 DUPLICATES REMOVED)
L12            7 SORT L11 PY
                E DUDLAND P?/AU
                E RUDLAND P?/AU
L13          175 S E5
L14          121 DUP REM L13 (54 DUPLICATES REMOVED)
L15           17 S L14 AND (SV40? OR MMTV? OR NEUROFILAMENT? OR NF-L OR TGF? OR
L16            4 S L15 AND TRANSGENIC
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=> d an ti so au ab pi l16 1 2

L16 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS
AN 1999:473378 CAPLUS
DN 131:284659
TI Development of hyperplasias, preneoplasias, and mammary tumors in **MMTV**-c-**erbB**-2 and **MMTV-TGF**.alpha. **transgenic** rats
SO Am. J. Pathol. (1999), 155(1), 303-314
CODEN: AJPAA4; ISSN: 0002-9440
AU Davies, Barry R.; Platt-Higgins, Angela M.; Schmidt, Gunter; **Rudland, Philip S.**
AB Human cDNAs corresponding to two epidermal growth factor-related products that are overexpressed in human breast cancers, that for c-**erbB** -2 (HER-2) and for transforming growth factor .alpha. (**TGF** .alpha.), have been cloned downstream of the mouse mammary tumor virus ( **MMTV**) long terminal repeat promoter and injected into the pronucleus of fertilized oocytes of Sprague-Dawley rats to produce **transgenic** offspring. Expression of the **transgenic** mRNAs is not detectable in mammary tissue from virgin **transgenic** rats but is detected in mammary tissue from certain lines of mid-pregnant **transgenic** rats. When two such lines of either type of **transgenic** rat are subjected to repeated cycles of pregnancy and lactation, they produce, primarily in the mammary glands, extensive pathologies, whereas virgin **transgenic** rats produce no such abnormalities. Multiparous **transgenic** female offspring from c-**erbB**-2-expressing lines develop a variety of focal hyperplastic and benign lesions that resemble lesions commonly found in human breasts. These lesions include lobular and ductal hyperplasia, fibroadenoma, cystic expansions, and papillary adenomas. More malignant lesions, including ductal carcinoma in situ and carcinoma, also develop stochastically at low frequency. The mammary glands of **transgenic** females invariably fail to involute fully after lactation. Similar phenotypes are obsd. in female **MMTV-TGF**.alpha. **transgenic** rats. In addn., multiparous **TGF**.alpha.-expressing female **transgenics** frequently develop severe pregnancy-dependent lactating hyperplasias as well as residual lobules of hyperplastic secretory epithelium and genuine lactating adenomas after weaning. These **transgenic** rat models confirm the conclusions reached in **transgenic** mice that overexpression of the c-**erbB**-2 and

**TGF**.alpha. genes predisposes the mammary gland to stochastic tumor development.

L16 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS
AN 1998:9289 CAPLUS
DN 128:73597
TI Induction of a variety of preneoplasias and tumors in the mammary glands of **transgenic** rats
SO Biochem. Soc. Symp. (1998), 63(Mammary Development and Cancer), 167-184
CODEN: BSSYAT; ISSN: 0067-8694
AU Davies, Barry R.; Warren, Joe R.; Schmidt, Gunter; **Rudland, Philip S.**
AB Although **transgenic** mouse models for breast cancer have frequently been reported in the literature, **transgenic** rat models have not been described. The authors have generated **transgenic** rats overexpressing the human transforming growth factor .alpha. (**TGF**.alpha.) and c-**erbB**-2 genes in the mammary gland under the control of the mouse mammary tumor virus ( **MMTV**) long terminal repeat promoter, and have analyzed multiple lines of these rats to the second (F2) generation. Female **MMTV**/**TGF**.alpha. rats frequently develop severe hyperplasias during pregnancy, and a variety of tumors of long latency. The mammary glands of **MMTV**/**TGF**.alpha. rats fail to involute fully after the completion of lactation. Expression of the **TGF**.alpha. transgene is highest in the hyperplasias. **MMTV**/c-**erbB**-2 female rats develop a spectrum of benign and malignant lesions, including ductal carcinoma in situ and carcinomas. Expression of the c-**erbB**-2 transgene is found in benign tumors such as fibroadenomas, but is highest in the carcinomas. These animals model a spectrum of lesions found in human breasts and suggest that **TGF**.alpha. overexpression can act at a relatively early stage in the pathogenesis of breast cancer in the rat, resulting in a predominantly hyperplastic response, whereas overexpression of c-**erbB**-2 plays a role in the induction of various benign lesions and more advanced breast carcinomas.

=> d an ti so au ab pi l12 2

L12 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 1997:696860 CAPLUS
DN 127:355930
TI Conditionally immortalized cell lines derived from transgenic animals and their toxicological and pharmacological uses
SO PCT Int. Appl., 85 pp.
CODEN: PIXXD2
IN Rudland, Philip Spencer; Barraclough, Barry Roger; Kilty, Iain Charles; Davies, Barry Robert; Schmidt, Guenter
AB Provided is a cell line derived from a transgenic animal comprising (1) a conditional oncogene, transforming gene or immortalizing gene or a cell cycle affecting gene; and (2) a cell type specific promoter. They include a neuronal cell line in which the cell type specific promoter is an **NF-L** gene promoter, and a mammary cell line in which the cell type specific promoter is a **MMTV** gene promoter. The conditional oncogene, transforming gene or immortalizing gene is preferably a SV40 tsA58 gene. Prodn. of transgenic Sprague Dawley rats by using mammary-targeting vector **MMTVLTRtsA58U19** (contg. **MMTV** Long Terminal Repeat) or brain-targeting vector NF-LtsA58.delta.t (contg. human **neurofilament** light chain promoter), and prepn. of cell lines B2LT1 and NF2C from the mammary of **MMTVLTRtsA58U19 transgenic rats** and the brain of NF-LtsA58.delta.t **transgenic rats**, resp., were shown. Prodn. of **transgenic rats** carrying oncogene such as c-erb.beta.-2 or transforming growth factor .alpha. (TGF.alpha.) that are highly assocd. with breast cancer was also shown. The transgenic

animals and their immortalized cell lines are useful for toxicol. and pharmacol. studies.

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9739117 | A1 | 19971023 | WO 1997-GB1063 | 19970417 |
| | W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| | AU 9725723 | A1 | 19971107 | AU 1997-25723 | 19970417 |
| | EP 904363 | A1 | 19990331 | EP 1997-917342 | 19970417 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| | JP 2000508897 | T2 | 20000718 | JP 1997-536877 | 19970417 |

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FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, BIOSIS, MEDICONF'
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L11          7 DUP REM L10 (12 DUPLICATES REMOVED)
L12          7 SORT L11 PY
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=> d an ti so au ab pi l12 1-6

L12 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 1993:401966 CAPLUS
DN 119:1966
TI Tissue-specific expression of rat light **neurofilament** promoter-driven reporter gene in transgenic mice
SO Biochem. Biophys. Res. Commun. (1993), 192(2), 465-70
CODEN: BBRCA9; ISSN: 0006-291X
AU Reeben, Mati; Halmekyto, Maria; Alhonen, Leena; Sinervirta, Riitta; Saarma, Mart; Janne, Juhani
AB Nine transgenic mice lines carrying either 5 kbp or 407 bp of the 5' flanking sequence of the rat light **neurofilament** gene linked to the chloramphenicol acetyltransferase (CAT) structural gene were produced. With the 5 kb light **neurofilament** 5' flanking region governing the expression of CAT, reporter gene activity was detected not only in brain but also in the eye lens and skeletal muscle, yet not in other tissues. With the 407 bp construct, reporter gene activity was detected only in the brain, although expression was approx. one tenth of that found with the 5 kb 5' region. These results, together with earlier observations, indicate that the sequence -407 to -292 of the proximal promoter region for the light **neurofilament** gene or sequence +15 to +75 bp after the transcription initiation site is crucial for brain-specific expression of a fusion gene in transgenic mice.

L12 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 1997:696860 CAPLUS
DN 127:355930
TI Conditionally immortalized cell lines derived from transgenic animals and their toxicological and pharmacological uses
SO PCT Int. Appl., 85 pp.
CODEN: PIXXD2
IN Rudland, Philip Spencer; Barraclough, Barry Roger; Kilty, Iain Charles; Davies, Barry Robert; Schmidt, Guenter
AB Provided is a cell line derived from a transgenic animal comprising (1) a conditional oncogene, transforming gene or immortalizing gene or a cell cycle affecting gene; and (2) a cell type specific promoter. They include a neuronal cell line in which the cell type specific promoter is an **NF-L** gene promoter, and a mammary cell line in which the cell type specific promoter is a **MMTV** gene promoter. The conditional oncogene, transforming gene or immortalizing gene is preferably a SV40 tsA58 gene. Prodn. of transgenic Sprague Dawley rats by using mammary-targeting vector **MMTVLTRtsA58U19** (contg. **MMTV** Long Terminal Repeat) or brain-targeting vector NF-LtsA58.delta.t (contg. human **neurofilament** light chain promoter), and prepn. of cell lines B2LT1 and NF2C from the mammary of

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**MMTVLTRtsA58U19 transgenic rats** and the brain of NF-LtsA58.delta.t **transgenic rats**, resp., were shown. Prodn. of **transgenic rats** carrying oncogene such as c-erb.beta.-2 or transforming growth factor .alpha. (TGF.alpha.) that are highly assocd. with breast cancer was also shown. The transgenic animals and their immortalized cell lines are useful for toxicol. and pharmacol. studies.

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9739117 | A1 | 19971023 | WO 1997-GB1063 | 19970417 |
| | W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| | AU 9725723 | A1 | 19971107 | AU 1997-25723 | 19970417 |
| | EP 904363 | A1 | 19990331 | EP 1997-917342 | 19970417 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| | JP 2000508897 | T2 | 20000718 | JP 1997-536877 | 19970417 |

L12 ANSWER 3 OF 7 MEDLINE
AN 1998174908 MEDLINE
TI Induction of a variety of preneoplasias and tumours in the mammary glands of **transgenic rats**.
SO BIOCHEMICAL SOCIETY SYMPOSIA, (1998) 63 167-84. Ref: 53
Journal code: 9ZK; 7506896. ISSN: 0067-8694.
AU Davies B R; Warren J R; Schmidt G; Rudland P S
AB Although transgenic mouse models for breast cancer have frequently been reported in the literature, **transgenic rat** models have not been described. We have generated **transgenic rats** overexpressing the human transforming growth factor alpha (TGF alpha) and c-erbB-2 genes in the mammary gland under the control of the mouse mammary tumour virus (**MMTV**) long terminal repeat promoter, and have analysed multiple lines of these rats to the second (F2) generation. Female **MMTV**/TGF alpha rats frequently develop severe hyperplasias during pregnancy, and a variety of tumours of long latency. The mammary glands of **MMTV**/TGF alpha rats fail to involute fully after the completion of lactation. Expression of the TGF alpha transgene is highest in the hyperplasias. **MMTV**/c-erbB-2 female rats develop a spectrum of benign and malignant lesions, including ductal carcinoma in situ and carcinomas. Expression of the c-erbB-2 transgene is found in benign tumours such as fibroadenomas, but is highest in the carcinomas. These animals model a spectrum of lesions found in human breasts and suggest that TGF alpha overexpression can act at a relatively early stage in the pathogenesis of breast cancer in the rat, resulting in a predominantly hyperplastic response, whereas overexpression of c-erbB-2 plays a role in the induction of various benign lesions and more advanced breast carcinomas.

L12 ANSWER 4 OF 7 MEDLINE
AN 2000005436 MEDLINE
TI Isolation of a potential neural stem cell line from the internal capsule of an adult **transgenic rat** brain.
SO JOURNAL OF NEUROCHEMISTRY, (1999 Nov) 73 (5) 1859-70.
Journal code: JAV; 2985190R. ISSN: 0022-3042.
AU Kilty I C; Barraclough R; Schmidt G; Rudland P S
AB A thermosensitive mutation of simian virus 40 large T antigen (LTA) gene, the tsA58 gene, was cloned downstream of the 6-kbp **neurofilament** light chain promoter in pPOLYIII and injected into the pronucleus of fertilised oocytes of Sprague-Dawley rats to develop a strain harbouring six copies of the transgene. Immunocytochemical staining of hemizygous

adult tissues with antibodies to the C-terminus of LTA showed that the inactive form of LTA was expressed only in the fibres of the internal capsule and in the choroid plexus of the brain. Culturing the former region at 33 degrees C, the permissive temperature for LTA, yielded a cell line, NF2C, which produced active LTA and grew at 33 degrees C but which produced only inactive LTA and eventually died at the non-permissive temperature of 39 degrees C. This clonal cell line was heterogeneous at 33 degrees C, producing the precursor neuronal cell marker nestin and the glial-specific markers glial fibrillary acidic protein, vimentin and S100A1, as well as weakly producing the neuronal cell markers 68-kDa **neurofilament** protein (NF68) and microtubule-associated protein 2 (MAP2) in different subpopulations of cells. However, at 39 degrees C, the cells produced dendritic, neuronal-like processes and elevated levels of NF68 and MAP2, as well as the neuronal markers synaptophysin, neurone-specific enolase, and low levels of tau, all determined by western blotting and immunofluorescent staining. Basic fibroblast growth factor enhanced the growth of the cells at 33 degrees C but also enhanced the formation of dendritic neuronal-like processes at 39 degrees C. It is suggested that NF2C represents a potential stem cell line from adult brain that expresses precursor and glial cell markers at 33 degrees C but undergoes partial differentiation to a neuronal cell phenotype at 39 degrees C.

L12 ANSWER 5 OF 7 MEDLINE
AN 1999324322 MEDLINE
TI Development of hyperplasias, preneoplasias, and mammary tumors in **MMTV**-c-erbB-2 and **MMTV**-TGFalpha **transgenic rats**.
SO AMERICAN JOURNAL OF PATHOLOGY, (1999 Jul) 155 (1) 303-14.
Journal code: 3RS; 0370502. ISSN: 0002-9440.
AU Davies B R; Platt-Higgins A M; Schmidt G; Rudland P S
AB Human cDNAs corresponding to two epidermal growth factor-related products that are overexpressed in human breast cancers, that for c-erbB-2 (HER-2) and for transforming growth factor alpha (TGFalpha), have been cloned downstream of the mouse mammary tumor virus (**MMTV**) long terminal repeat promoter and injected into the pronucleus of fertilized oocytes of Sprague-Dawley rats to produce transgenic offspring. Expression of the transgenic mRNAs is not detectable in mammary tissue from virgin **transgenic rats** but is detected in mammary tissue from certain lines of mid-pregnant **transgenic rats**. When two such lines of either type of **transgenic rat** are subjected to repeated cycles of pregnancy and lactation, they produce, primarily in the mammary glands, extensive pathologies, whereas virgin **transgenic rats** produce no such abnormalities.
Multiparous transgenic female offspring from c-erbB-2-expressing lines develop a variety of focal hyperplastic and benign lesions that resemble lesions commonly found in human breasts. These lesions include lobular and ductal hyperplasia, fibroadenoma, cystic expansions, and papillary adenomas. More malignant lesions, including ductal carcinoma in situ and carcinoma, also develop stochastically at low frequency. The mammary glands of transgenic females invariably fail to involute fully after lactation. Similar phenotypes are observed in female **MMTV**-TGFalpha **transgenic rats**. In addition, multiparous TGFalpha-expressing female transgenics frequently develop severe pregnancy-dependent lactating hyperplasias as well as residual lobules of hyperplastic secretory epithelium and genuine lactating adenomas after weaning. These **transgenic rat** models confirm the conclusions reached in transgenic mice that overexpression of the c-erbB-2 and TGFalpha genes predisposes the mammary gland to stochastic tumor development.

L12 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 1999:253466 CAPLUS
DN 131:126052
TI Production of **transgenic rats** and mice by the

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testis-mediated gene transfer
SO J. Reprod. Dev. (1999), 45(1), 29-36
CODEN: JREDEF; ISSN: 0916-8818
AU Chang, Kyu-Tae; Ikeda, Akihiro; Hayashi, Katsuhiko; Furuhata, Yasufumi; Nishihara, Masugi; Ohta, Akihiko; Ogawa, Shyoso; Takahashi, Michio
AB Recent reports have shown that sperm cells incubated with foreign DNA in vitro are able to transfer the DNA into eggs at fertilization. The present study examd. if an injection of DNA into the testis in vivo could generate transgenic animals via sperm ejaculated. We prepd. 3 gene constructs; human growth hormone (hGH), hGH receptor (hGHR) and mouse leptin (mOB) genes fused to the promoter regions of the mouse genes for whey acidic protein (WAP), metallothionein-I (MT) and mouse mammary tumor virus (**MMTV**), resp. Each gene construct mixed with cationic liposome was injected into bilateral testes of male rats or mice, and the males mated with females 3 or 4 days later. A female rat mated with a male treated with MT/hGHR gene gave birth to 17 pups, 3 of which were found to carry the transgene. The expression of hGHR mRNA was demonstrated in the liver, kidney, muscle and brain after treating with zinc in drinking water. At present, the transmission of the exogenous gene to the descendants was confirmed up to the F4 generation. Three female rats mated with 3 different males injected with **MMTV**/mOB fusion gene produced 10, 14 and 12 pups, resp. The genome of 2 out of these 36 pups harbored **MMTV**-mOB gene, though expression of mOB mRNA was not detected. Two female mice were mated with 2 male mice injected with WAP/hGH gene and produced 15 and 16 pups, 3 of which incorporated the gene. The expression of hGH mRNA in the mammary gland in these mice was confirmed. These results indicate that exogenous DNA injected into the testis as a liposome-complex can be transferred into eggs via sperm and expressed in the postpartum progeny.

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L12 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:547555 BIOSIS
TI Transgenic animal models in studies of biochemical pathways of progressive myoclonus epilepsy (EPM1.
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 1469. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
AU Arbatova, J. (1); Alhonen, L.; Kalda, A.; Zharkovsky, A.; Jolkkonen, J. (1); Reeben, M. (1)
AB Defects in a cysteine proteinase inhibitor of cathepsins, cystatin B (CSTB) gene are responsible for progressive myoclonus epilepsy of Unverricht-Lundborg type (EPM1)-an autosomal recessive neurodegenerative disease. The mechanisms how lack of CSTB causes the disease phenotype are still poorly understood. CSTB-deficient mice (Pennacchio et al., Nature Genetics, 20, 251-8,1998) the mouse model of EPM1 provided evidence that CSTB could have a role in preventing neuronal apoptosis. We have produced **transgenic rats** that overexpress CSTB in the nervous system under the control of the rat light **neurofilament** gene regulatory regions and demonstrated that cerebellar granule cells from **transgenic rats** were more sensitive to the neurotoxic effects of glutamate and colchicine as compared with wild-type littermates. When these rats were exposed to transient focal cerebral ischemia by occluding the middle cerebral artery for 120 min, **transgenic rats** showed a trend towards a more severe cortical damage measured on day 22 after ischemia and a more severe impairment in sensorimotor functions as assessed by the limb-placing test. These results are contradictory to our hypothesis of a neuroprotective role of CSTB. An explanation for these results could be that a disbalance between protease inhibition (CSTB) and proteases (cathepsins) due to CSTB overexpression is also harmful. Currently, we are studying metabolites in

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serum and CSF of EPM1 patients and in tissues of knockout mice.

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